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Update on etiopathogenesis, clinical signs and diagnosis of diabetes in cats

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Diabetes mellitus is a common endocrine disease in cats. It is currently assumed that approximately 80% of diabetic cats suffer from a type 2 like diabetes, which is a heterogeneous disease due to a combination of insulin resistance and β-cell failure. Risk factors are obesity, increasing age, male gender, being neutered, physical inactivity, glucocorticoid and progestin administration, and being a Burmese cat (at least in some countries). Other specific types of diabetes (formerly called secondary diabetes) account for approximately 20% of cases and include pancreatitis, hyperadrenocorticism, hypersomatotropism and the application of progestins or glucocorticoids.
Diabetes typically occurs in middle-aged to old cats, with a strong sex predilection for males. Approximately 60% of diabetic cats are overweight, 35% are normal weight and 5% underweight. Most diabetic cats have the classical symptoms of diabetes, namely polyuria, polydipsia, polyphagia and weight loss. About 10% have overt symptoms of diabetic neuropathy, manifested as hind limb weakness, decreased ability to jump and plantigrade posture. Cats are prone to stress hyperglycemia which has to be differentiated from hyperglycemia due to diabetes by repeated blood glucose measurements or by measurement of fructosamine. Fructosamine is the product of an irreversible reaction between glucose and the amino groups of plasma proteins. Based on the lifespan of plasma protein, fructosamine concentration reflects the mean blood glucose concentration of the preceding 1 – 2 weeks. Reference ranges differ slightly between laboratories but are usually between 200 and 360 µmol/l. In the vast majority of newly diagnosed diabetic cats, fructosamine levels are > 400 µmol/l and may be as high as 1500 µmol/l. Fructosamine is not affected by short-term increases in blood glucose concentration and thus is usually normal in cats with stress hyperglycemia.
However, fructosamine is not a foolproof parameter and certain aspects need to be considered for its use as a diagnostic and monitoring parameter. In-vitro and in-vivo studies have shown that for fructosamine to increase above the upper limit of the reference range, marked hyperglycemia (> 22 mmol/l, 400 mg/dl) must be present for at least 3 – 5 days. In cats with moderate hyperglycemia, the respective time period is longer, for example up to 14 days when the average blood glucose concentration is 17 mmol/l (300 mg/dl). Therefore, cats with a very recent onset of diabetes or with mild diabetes may have normal fructosamine levels. Fructosamine is also influenced by plasma protein concentration and by protein turnover and diabetic cats with concurrent hypoproteinemia or hyperthyroidism may have normal fructosamine levels, which is misleading.
Further work-up should clarify the severity of diabetes, presence of concurrent disease and presence of underlying disease/factors. Treatment should be initiated immediately and include twice daily insulin application (intermediate acting insulin) and high-protein-low carbohydrate diet.
The general aim of therapy is to provide a good quality of life by eliminating clinical signs of diabetes and preventing complications such as hypoglycemia and ketoacidosis. Insulin is the mainstay of therapy and is superior to oral hypoglycemic drugs to reverse the effects of glucose toxicity and to increase the likelihood of diabetic remission. Currently there are 6 classes of oral agents approved for use in human diabetics and various others are under investigation. With the exception of sulfonylureas they have either not been investigated in

diabetic cats (meglinitieds, thiazolidinedionses, incretins) or have shown to be of only limited effect rendering them unsuitable for sole use (biguanide, α-glucosidase inhibitor). Sulfonylurease i.e. glipizide is effective in only approximately 30% of cats, which is too low to be recommended as a useful treatment option.

In the last two decades, the manufacture and development of insulin for human use has undergone revolutionary changes, which have had important implications in veterinary medicine. First, insulins derived from animal sources are being replaced by recombinant human preparations and will eventually disappear from the market. Fortunately, although feline insulin differs considerably from human insulin, it is biologically active, and the risk of anti-insulin antibodies interfering with glycemic control seems to be low.

Second, insulin preparations for human use containing 40-IU/ml have largely been replaced by 100- IU/ml insulins. It is important that owners understand the difference because insulin preparations for veterinary use (Caninsulin, Pro Zinc) is supplied as 40-IU/ml, requiring other syringes than for the human insulin. Third, new classes of insulins called insulin analogs have been developed. They were designed to improve the pharmacodynamic properties of insulin and render more predictable insulin absorption and/or insulin degradation. The currently available insulin analogs (Lantus, Determir) are just the start of a whole new area of insulin preparations.

Cats are unpredictable in their response to insulin and none of the insulins described above are routinely effective to control the disease. At the University of Zurich, treatment is started with Lantus. The reason for this choice is that retrospective analysis of our data base revealed, that remission rate in cats treated with Lantus compared to cats treated with Caninsulin was higher. In principle Caninsulin is also an appropriate choice, however, in some cats duration of action is too short and response may be unpredictable. Pro Zinc has recently been shown to also be an effective insulin (in dogs), but it is currently still difficult/impossible to obtain in Europe and therefore not routinely used. Frequency of administration is always BID. The initial dose in cats weighing $\leq$ 4 kg is 1 U/cat BID, and in cats weighing > 4kg it is usually 1.5 – 2.0 U/cat BID. In cats with a blood glucose concentration < 20 mmol/l at the time of diagnosis, no more than 1 U/cat BID is given, independent of the body weight.

Initially, frequent re-evaluations should be scheduled, with time, intervals can be extended. In our hospital re-evaluations are suggested 1, 3, 8, 12 weeks after diagnosis and then approximately every 4 months.

The owner should assess his animal with regard to the clinical signs of diabetes mellitus on a daily basis. Body weight should be taken at least once a week. It is important that the owner is familiar with the clinical signs of the most important complications of diabetes mellitus, i.e. hypoglycemia and diabetic ketoacidosis. In general, single measurements are considered insufficient to assess metabolic control. Blood glucose curves (BGCs) are necessary to evaluate insulin efficacy, glucose nadir, duration of insulin effect, degree of fluctuation and the Somogyi effect. We prefer that owners give insulin and food at home and then bring the animal quickly to the hospital (within 2 hours) for a BGC. This approach eliminates the effect of lack of food intake on blood glucose levels, at least in animals which are only fed at the time of insulin administration.

However, the procedure is time-consuming and expensive and therefore in many patients may not be carried out as often as indicated and the concentration of blood glucose can be markedly influenced by the stress of hospitalisation. We therefore recommend to the owners of diabetic cats to perform so-called home monitoring (HM) of capillary blood glucose and approximately 70% of the owners are willing and able to do this. Usually, we introduce HM 3 weeks after the initial presentation.

Capillary blood is obtained from the pinna or paw and glucose is determined with a portable glucometer (PBGM). Owners can certainly be taught to interpret a BGC; however, we prefer that decisions regarding changes in the insulin dose be made by the veterinarian and therefore,

BGCs be sent to the hospital. Ideally, the glucose concentration ranges from 12 – 15 mmol/l before the insulin injection with a nadir from 5 – 9 mmol/l. A low nadir may occur in insulin overdose (including sudden improvement of insulin-resistant states), excessive overlap of insulin actions and lack of food intake. If the nadir is > 9 mmol/l, insulin underdose, the counter-regulatory phase of the Somogyi effect and technical problems involving the injection of insulin by the owner must be considered. In diabetic pets that already receive high doses of insulin (> 1.5 U/kg/injection), concurrent diseases causing insulin resistance are also possible. The duration of effect is defined at the time from insulin injection through the glucose nadir until the blood glucose concentration exceeds 12 – 15 mmol/l. If the duration is less than 8 – 10 hours, the animal usually has signs of diabetes and if the duration is longer than 14 hours and the insulin is given twice daily, the risk of hypoglycemia increases. In humans, it is well known that blood glucose concentrations can vary markedly from day to day. There is also a high degree of variability among BGCs of diabetic pets. One of the major advantages of HM is that it enables frequent generation of BGCs, which may be of particular importance in animals that are difficult to regulate. In those cases, more than one BGC can be generated at home before a change in treatment is initiated. HM has replaced measurement of urine glucose nearly completely in our hospital.
We routinely measure the fructosamine concentration during the re-evaluations. It increases when glycemic control worsens and decreases when glycemic control improves. Since even well-controlled pets may be slightly too moderately hyperglycemic throughout the day, fructosamine concentrations will not usually decrease into the normal range. On the contrary, a normal fructosamine concentration should raise concern about prolonged periods of hypoglycemia (insulin overdose, diabetic remission). Metabolic control is usually good when fructosamine levels are between 350 and 450 µmol/l, moderate when values are between 450 and 550 µmol/l and poor when levels are > 550 – 600 µmol/l.

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